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Clinical Improvement in Hypertrophic Cardiomyopathy After Inferior Myocardial Infarction

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In cases of hypertrophic cardiomyopathy, the pathophysiologic role of the systolic pressure gradient across the left ventricular outflow tract is the subject of continued controversy. A patient with this disorder is described whose symptoms and provokable intraventricular gradient disappeared after inferior myocardial infarction. Diastolic left ventricular pressures were essentially unchanged, the isovolumic relaxation period became prolonged and the ejection fraction decreased from 0.77 to 0.61 after infarction. The peak ejection rate was unchanged, but the disappearance of systolic anterior motion of the mitral valve leaflet and obstructive manifestations may have resulted from enlarged mid to late systolic ventricular volumes. This case suggests a direct relation between symptoms and intraventricular pressure gradient in certain patients with hypertrophic cardiomyopathy.

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Hypertrophic cardiomyopathy is a genetically influenced disorder characterized by ventricular hypertrophy that is often asymmetrically distributed (1,2) and microscopically disorganized (1,3). A mid to late systolic murmur and an intraventricular pressure gradient may be present at rest or with provocation. However, because the left ventricle empties more completely and with higher peak flow than normal, the existence of true obstruction to outflow has been questioned (4) and this controversy remains unsettled (5). Although dyspnea, angina and syncope do not correlate directly with the intraventricular gradient (6), medical (7–9) and surgical (10) interventions that palliate symptoms generally also reduce or abolish this dynamic pressure gradient. The spontaneous clinical improvement after myocardial infarction in a patient with hypertrophic cardiomyopathy, with concomitant reduction in obstructive manifestations, provides additional indirect evidence that the intraventricular pressure gradient is not merely an epiphenomenon in this disorder (5,11).

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Case History

A 58 year old white man was readmitted to our facility for reevaluation of hypertrophic cardiomyopathy. Six years earlier, he had presented with a 2 year history of exertional chest oppression, limb fatigue and dyspnea. The exertional symptoms usually resolved after 30 minutes of rest; he also experienced postural light-headedness and occasional syncope.

Clinical features. *Physical examination* featured a prominent jugular A wave, bifid carotid pulse, double apical impulse, prominent S_4 and a grade 3/6 mid-systolic murmur that increased with the Valsalva maneuver and decreased with handgrip and squatting. The electrocardiogram showed left atrial enlargement and prominent left ventricular hypertrophy. M-mode echocardiography demonstrated asymmetric septal hypertrophy and marked systolic anterior motion of the anterior mitral leaflet (Fig. 1).

Transseptal cardiac catheterization revealed mild elevation in mean left atrial pressure, more prominent left ventricular end-diastolic pressure elevation and a provokable intraventricular gradient (Table 1). A 30° right anterior oblique left ventricular cineangiogram showed a rapidly contracting ventricle with an ejection fraction of 0.77, but without total apical systolic obliteration or mitral regurgitation. Despite a history of heavy smoking, the patient's coronary arteries were normal except for mild irregularities including a 20% narrowing of the left ventricular extension branch of the dominant right coronary artery.

The patient received propranolol, 320 mg/day, along with a thiazide diuretic drug for hypertension. However, he re-

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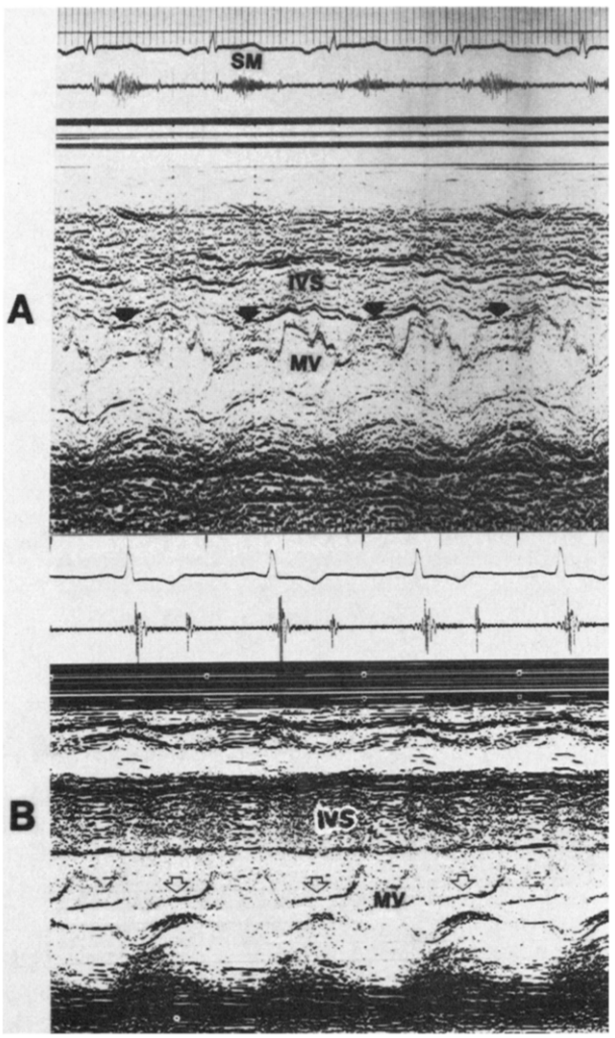


Figure 1. M-mode echocardiograms before (**A**) and after (**B**) myocardial infarction. In **A**, the **dark arrows** mark mitral valve (MV) systolic anterior motion, which coincides with the mid-systolic murmur (SM). In **B**, the systolic anterior motion (**open arrows**) and systolic murmur are absent. IVS = interventricular septum.

mained in New York Heart Association functional class III because of dyspnea and angina. His blood pressure generally was 150/90 mm Hg on follow-up, and his murmur at rest was unchanged during the drug therapy.

Clinical course after myocardial infarction. The patient remained clinically unchanged until 6 years after his initial presentation, when he was admitted to another hospital for severe crushing retrosternal chest pain. Inferior myocardial infarction was diagnosed by electrocardiographic Q waves, creatine kinase isoenzyme elevation and technetium pyrophosphate scintigraphic scan. The hospital course was uncomplicated, and he was discharged while taking propranolol and a thiazide diuretic drug.

After recovering from his infarction, the patient stated without prompting that his oppressive symptoms had vanished almost entirely. Only a "slight twinge of limb heaviness" occurred during heavy exertion, without the troubling dyspnea or angina, allowing much improved exercise tolerance. On admission 2 months after his infarction, physical examination revealed a palpable S_4, normal carotid pulse and no murmur at rest or with the Valsalva maneuver. The electrocardiogram showed new deep inferior Q waves and anterolateral T wave inversions. M-mode echocardiography demonstrated complete disappearance of mitral systolic anterior motion (Fig. 1). Two-dimensional echocardiography clearly showed mitral leaflet coaptation at the midportion of the anterior leaflet (12), with the distal anterior leaflet freely floating in the left ventricle but not moving toward the septum during systole. Propranolol was withheld for 24 hours, and repeat transseptal cardiac catheterization showed essentially unchanged diastolic pressures and no provokable intraventricular gradient (Table 1). The repeat 30° right anterior oblique left ventricular angiogram showed an inferobasal dyskinetic segment, an ejection fraction of 0.61 and no mitral regurgitation. Coronary angiography showed a new subtotal occlusion in the left ventricular extension branch of the right coronary.

Data analysis. Frame by frame left ventricular volumes were calculated with a lightpen-accessed Dodge area-length program (two tracings averaged for each frame), and the first well opacified beat was analyzed in the pre- and post-infarction studies (Fig. 2). There was no ventricular arrhythmia during either cineangiogram, but poorly defined aortic valve closure did not allow definition of end-systole. In addition, the isovolumic relaxation time was measured from the first high frequency component of S_2 to the point of initial rapid mitral opening on simultaneous phonocardiography and echocardiography, averaged over four beats and rounded to the nearest 10 ms before and after infarction (Fig. 1, Table 1).

Discussion

Arguments for obstruction to outflow. The constellation of dyspnea, angina, syncope, systolic murmur, asymmetric septal hypertrophy, systolic anterior motion of the mitral valve and provokable intraventricular gradient in this patient is typical of hypertrophic cardiomyopathy (11). In the preinfarction basal state, the peak left ventricular ejection rate was elevated (Fig. 2, Table 1). Careful electromagnetic flow probe and angiographic studies (13) have demonstrated similarly elevated peak ejection rates in cases of hypertrophic cardiomyopathy with or without an intraventricular pressure gradient at rest, and these findings have been interpreted as evidence against true obstruction to outflow. A comprehensive account of hypertrophic cardiomyopathy, however, must acknowledge that the systolic pressure in nonobliterated portions of the left ventricle may be far in excess of that in the outflow tract or aorta during

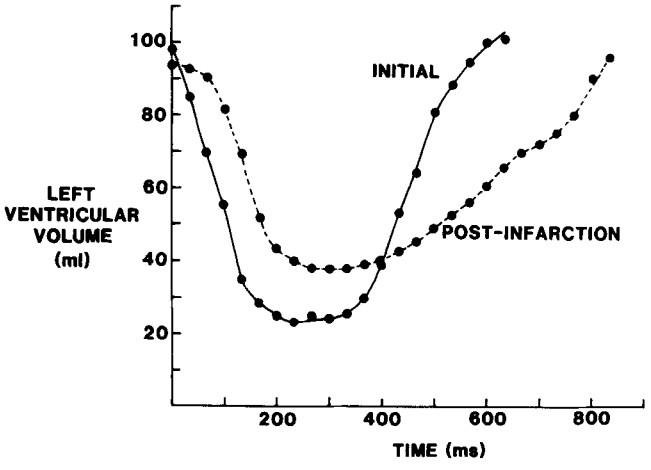
Table 1. Hemodynamic Profile in Patient With Hypertrophic Cardiomyopathy Before and After Myocardial Infarction

	Initial Study	Postinfarction
Pressure (mm Hg)	25/15 [14]	32/18 [15]
Left atrium (A wave/V wave [mean])		
Control		
Left ventricle (systolic/mid-diastolic/end-diastolic)	178/16/24	165/14/27
Aorta (systolic/diastolic)	174/110	180/95*
Valsalva (phase 2)		
Left ventricle (systolic)	202	150
Aorta (systolic/diastolic)	130/100	150/100
Isoproterenol infusion (heart rate [beats/min])	(82→98)	(60→108)
Left ventricle (systolic/mid-diastolic/end-diastolic)	270/20/35	148/10/16
Aorta (systolic/diastolic)	140/100	148/100
Maximal intraventricular gradient	172†	0‡
Rest heart rate (beats/min)	82	60
Cardiac index (liters/min per m^2)	2.7	1.9
Left ventricular ejection fraction	0.77	0.61
Peak ejection rate (ml/s)	480	450
Isovolumic relaxation time (ms)	40	100

*Femoral artery pressure; †premature ventricular complex during the Valsalva maneuver; ‡including premature ventricular complex and Valsalva maneuvers during isoproterenol infusion.

a portion of ventricular ejection (14). In this case, for instance, the preinfarction left ventricular peak systolic pressure carefully measured just within the mitral inlet was 270 mm Hg during isoproterenol infusion compared with an aortic systolic pressure of 140 mm Hg. According to basic hydraulic principles, such a pressure gradient during flow reflects an abnormal resistance to ejection (15). Because a portion of ejection occurs before a high outflow gradient is reached, the effect on stroke work (as estimated by the time average of instantaneous ejection volume times outflow gradient) is less than that due to a fixed obstruction (16). In support of obstruction, nevertheless, is that the time required to complete ejection tends to be longer with than without an intraventricular gradient (13), in the extreme case manifesting with reversed splitting of S_2 (6,17), and several methods of measurement show a low magnitude plateau after the early peak in aortic flow (16,18,19).

Figure 2. Angiographic left ventricular volume-time curves before and after myocardial infarction.



Systolic phenomena. The systolic pressure within the body of the left ventricle may be strikingly elevated, but when expressed as systolic wall stress (for example, equatorial midwall), instantaneous left ventricular load depends on ventricular geometry as well as the intracavitary pressure (20). Simplified geometric assumptions are not readily applicable in the asymmetrically hypertrophied ventricle, but both an increase in mean wall thickness and a decrease in ventricular radius presumably would reduce systolic stress for a given ventricular pressure (21). Because patients with an intraventricular gradient at rest tend to have more generalized hypertrophy than do those without (2), the unloading effect of such hypertrophy may help explain the comparable peak rate and completeness of ejection in the two groups (13,21). Indeed, certain patients with fixed aortic stenosis have a supernormal ejection fraction (22,23), presumably because hypertrophy reduces systolic ventricular stress (23).

Marked elevation of systolic ventricular pressure may have other consequences. For instance, reflex changes due to elevated ventricular pressure may play a role in syncope, as suggested in cases of aortic stenosis (24). Furthermore, because coronary flow reserve may be reduced in hypertrophic states (25), the moderate effects of dynamic obstruction on stroke work and myocardial oxygen requirements may be sufficient to produce ischemia. Angina and dyspnea sometimes exist in the absence of a demonstrable intraventricular gradient (6), but our patient's symptoms im-

proved dramatically with the disappearance of the provokable gradient, suggesting a causal relation in some instances. In a study (26) of 126 patients with hypertrophic cardiomyopathy, the average intraventricular gradient was significantly higher in those in functional classes III and IV than in those in classes I and II. In cases of fixed aortic stenosis, there is also only a rough correlation between the transaortic gradient and symptoms (27), suggesting that other variables such as coronary flow reserve have an important effect (25).

Diastolic abnormalities. Long recognized diastolic abnormalities in cases of hypertrophic cardiomyopathy have received recent emphasis (5,11,28–31). Normal to reduced diastolic ventricular volumes exist at elevated diastolic pressures, owing perhaps to the effects of increased wall thickness and abnormal relaxation on the diastolic pressure-volume relation (29,30,32). Although left ventricular end-diastolic pressure at rest is often elevated, there is poor correlation with functional class (26), and the mid-diastolic pressure, which better correlates with pulmonary congestion, may or may not be elevated. In this patient, for instance, the mean left atrial pressure at rest was mildly elevated both before and after infarction.

A prolonged isovolumic relaxation time has been cited as evidence of abnormal ventricular relaxation (29,30) and found to correlate roughly with the presence of angina (29). However, this time interval depends on the aortic- and mitral-left ventricular pressure crossover points, as well as on the ventricular pressure decay time. In a recent study (17) of 84 patients with hypertrophic cardiomyopathy, the isovolumic relaxation period varied widely from 0 to 160 ms, overlapping considerably with the normal range of 40 to 80 ms, and correlated poorly with symptoms. Reversed splitting of S_2 was found in the subset in which this interval was abnormally shortened; the delay in aortic closure correlated with a delay in left ventricular-aortic pressure crossover in the setting of a large intraventricular gradient, attesting to the reality and obstructive implications of such a gradient (17). In our patient, the isovolumic relaxation period was normal in the symptomatic preinfarction state, but somewhat prolonged after symptoms disappeared after infarction (Table 1), perhaps influenced by the reduction in heart rate (33). Thus, characterizing diastolic abnormalities in hypertrophic cardiomyopathy is difficult, and a simple variable like the isovolumic relaxation period shows no better correlation with symptoms than does the intraventricular pressure gradient.

Mechanism of obstruction. Production of the intraventricular pressure gradient appears to require systolic anterior motion of mitral valve tissue and septal contact (34,35). The distal portion of the anterior mitral leaflet often appears very loosely tethered (12), as in this case, and may be particularly susceptible to Venturi forces near the septum during the rapid phase of ejection (36). The mechanism of mitral systolic anterior motion is poorly understood, but because it occurs in hyperdynamic as well as hypertrophic states (37), a reduced ventricular systolic volume and a high early ejection rate are apparently needed. Understandably, these paradoxic requirements for a dynamic obstructive mechanism have led to conceptual difficulties, and they emphasize the fundamental differences with fixed outflow obstruction. In this patient, the peak flow rate was essentially unchanged after infarction, but the increase in mid- to end-systolic volumes may have prevented the provokable intraventricular gradient. The position of the posteromedial papillary muscle also may have been altered by the adjacent inferobasal infarction, but because loose tethering of the distal anterior mitral leaflet persisted after infarction, this potential effect was probably not important.

Related case reports. Although coronary artery disease and hypertrophic cardiomyopathy can coexist (38), some authorities (11) have been impressed by the rarity of this association. We are aware of only two other reports in which the provokable intraventricular gradient disappeared after infarction (39,40); in neither case was a symptomatic change mentioned. The traditional view that the hypertrophied septum is akinetic has been questioned (41), and in one of these cases an anteroseptal infarct resulted in a loss of obstructive manifestations (40). Our patient received a thiazide diuretic drug on a long-term basis for concomitant hypertension. Although the attendant decrease in vascular volume conceivably may exacerbate obstructive manifestations (16), there was no clinical evidence for such an adverse effect. Thiazide diuretic drugs cause only a 10 to 15% reduction in plasma volume (42) and, aside from a case involving both digitalis and diuretic drugs (43), we are unaware of reports detailing clinical deterioration in cases of hypertrophic cardiomyopathy as a result of diuretic drugs.

Therapeutic considerations. In the absence of an ideal therapy that reverses the underlying hypertrophic process, medical therapy palliates symptoms by reducing the inotropic state (7–9) or improving diastolic performance (31). Septal myectomy appears to be superior in reducing symptoms, but the high rates of morbidity and mortality are prohibitive (44), especially because there is little if any impact on the occurrence of subsequent sudden death (44,45). Maximal medical management, therefore, should be given before considering the surgical method (44). Diastolic ventricular pressures may sometimes be reduced, but the chief palliative mechanism of myectomy appears to be abolishment of the intraventricular gradient (10). In view of this and other cases (39,40), the possibility that controlled infarction with temporary coronary artery balloon occlusion may provide another palliative modality is intriguing and deserves further study. Aside from troublesome conceptual problems that remain, a large body of direct and indirect observation suggests a pathophysiologic role for the intra-

ventricular pressure gradient in hypertrophic cardiomyopathy. Therapies that have an impact on this facet of the disorder will continue to play an important part in its treatment.

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